227. The method of claim 200, 201, 207, 208, 215 or 216, wherein said subject is a human infant.

228. The method of claim 227, wherein said subject is a human infant born prematurely or is at risk of hospitalization for a RSV infection.

B8 cancel

229. The method of claim 200, 201, 207, 208, 215 or 216, wherein said palivizumab or fragments are administered 1, 2, 3, 4, or 5 times during the RSV season.

230. The method of claim 200, 201, 207, 208, 215, or 216, wherein said palivizumab or fragments are administered in a sustained release formulation.--

REMARKS

The specification has been amended to correct a typographical error in the Abstract. In addition, Applicants have also amended the Abstract to better summarize the claimed subject matter. Further, Applicants have amended the specification to recite the generic name of the antibody otherwise identified in the specification under the tradename SYNAGIS®. As such, the amendments do not constitute new matter as defined in 35 U.S.C. § 132. A marked up version of the Abstract of the specification, with the amendment indicated by underlining for additions, is attached hereto as Exhibit A. A "clean" copy of the Abstract of the specification, as amended, is attached hereto as Exhibit B.

Claims 1-72, 75-84, 111-179, 182-185, 188, and 192-199 have been canceled, without prejudice. The claims have not been canceled in response to any of the Examiner's rejections or objections. Rather, Applicants have canceled the claims merely to expedite prosecution and reserve the right to prosecute the subject matter of claims 1-72, 75-82, 111-179, 182-185, 188, and 192-199 or any other unclaimed subject matter, in one or more related applications. Claims 73-74, 85-88, 180, 181, and 186-187 have been amended to more particularly point out and distinctly claim the subject matter that Applicants regard as their invention. A marked up version of the amended claims indicating the changes is attached hereto as Exhibit C. Applicants have also added new claims 200 to 230 to more particularly point out and distinctly claim the subject matter which Applicants regard as their invention. The amended claims and new claims are fully supported in the specification as filed, and no new matter is introduced (*e.g.*, see the specification at page 9, line 10 to page 10, line 24; at

page 20, lines 19-22; at page 23, lines 4-11; at page 33, line 30 to page 35, line 18; and page 82, lines 11-27). Thus, upon entry of the present amendments, claims 73, 74, 85-110, 180, 181, 186, 187, 189-191, and 200-230 will be pending. For the Examiner's convenience, a copy of all pending claims is attached hereto as Exhibit D.

Objection to the Specification

The Examiner objects to the specification because the last sentence of the Abstract of the disclosure on page 149 of the specification lacks a period. Accordingly, Applicants have corrected the typographical error, thus obviating the objection, and request that the replacement Abstract be entered into the specification by amendment and objection be withdrawn.

Objection to the Claims

The Examiner indicates that claims 45-46 each contains a minor grammatical error. The Examiner has also indicated that Claim 198 has two periods at the end of the claim. Applicants have canceled claims 45-46 and 198 without prejudice and Examiner's objections are thereby rendered moot.

The Rejections Under 35 U.S.C. § 112, Second Paragraph Should Be Withdrawn

The Examiner has rejected claims 18, 44-72, 77, 78, 81-122, 139, 140-161, 168-179, and 193-199 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Preliminarily, Applicants note that in the interest of expediting prosecution, Applicants have chosen to cancel claims 18, 44-72, 77, 78, 81-84, 111-122, 139, 140-161, 168-179, and 193-199 without prejudice, reserving the right to pursue them in one or more related applications. Thus, the Examiner's rejection of these canceled claims under 35 U.S.C. § 112, second paragraph, is rendered moot. However, Applicants address below the Examiner's rejections to avoid having such a rejection applied to any non-canceled claims or pending new claims.

With respect to the Examiner's objections to claims 83, 84, 140-148, 156-161, and 168-179 in that the claims recite "increased" half-lives, Applicants disagree; however, as

noted above, in the interest of expediting prosecution, claims reciting "increased" half-lives have been canceled without prejudice and no pending claims recite "increased" half-lives. Accordingly, Applicants respectfully submit that the Examiner's rejection based on the term "increased" is rendered moot and should be withdrawn.

The Examiner also objects to claims 18, 44, 72, 77, 78, 81, 82, 85-122, 139, 149-155, and 193-199 in that the claims contain the trademark/trade name SYNAGIS® or HL SYNAGIS®. Claims which recite HL SYNAGIS® have been canceled without prejudice, thereby rendering the Examiner's objection moot for said claims. With respect to claims 85-110 and pending new claims, rather than using the term SYNAGIS®, the amended and new claims recite "palivizumab." Palivizumab is the generic name that is used interchangeably with its tradename SYNAGIS® and therefore the amendment does not constitute new matter, *see, e.g.*, MedImmune package insert cited by Examiner Brown. Applicant also notes that "palivizumab" and "SYNAGIS®" are also used interchangeably with "MEDI-493" by those skilled in the art. In view of the foregoing amendment, Applicants submit that the Examiner's objection has been obviated and request the rejection based on the recitation "SYNAGIS®" be withdrawn.

In addition, the Examiner also objects to claims 45-72, 85-110 and 140-158 in that these claims recite the phrases "prophylactically effective" and "therapeutically effective." The Examiner alleges that the claims are rendered indefinite because the claims do not define endpoints that indicate effectiveness has been achieved.

Preliminarily, Applicants respectfully submit that, contrary to the Examiner's position, the claims need not define endpoints that indicate effectiveness has been achieved by reciting specific serum titers. Applicants remind the Examiner that similar phrases such as "effective amount" have been held by courts to be definite where those skilled in the art would be able to determine from the written disclosure what an effective amount is by understanding the function to be achieved or the uses affected. *See, e.g., In re Halleck*, 422 F.2d 911 (CCPA 1975); *Ex parte Skuball*, 12 USPQ2d 1570 (Bd. Pat. App. & Inter. 1989).

More significantly, Applicants respectfully submit that one skilled in the art would understand the scope of the phrases "prophylactically effective" and "therapeutically effective" and that the scope of the claims is clear because the specification provides a definition of each phrase at page 29, line 26 to page 30, line 2 and at page 30, lines 3 to 15, respectively. "Prophylactically effective" serum titers reduce the incidence of a RSV infection in a mammal. "Therapeutically effective" serum titers reduce the severity, the

duration and/or the symptoms associated with a RSV infection in a mammal. Furthermore, Applicants submit that the specification describes assays for determining therapeutic or prophylactic utility, *e.g.*, assays for determining or achieving "prophylactically effective" and "therapeutically effective" serum titers (*see generally* specification at page 94, line 30 to page 100, line 8.) In view of the foregoing, Applicants request that the rejection under 35 U.S.C. § 112, second paragraph, of the claims based on the recitation "prophylactically effective" or "therapeutically effective" be reconsidered and withdrawn.

The Rejection Under 35 U.S.C. § 102 Should Be Withdrawn

The Examiner has rejected claims 1-9, 14-17, 74, 76 and 80 under 35 U.S.C. § 102(b) as being anticipated by Brams *et al.* (U.S. Patent 5,811,524; "Brams"). Claims 1-9, 14-17, 76 and 80 have been canceled without prejudice, rendering the rejection of said claims is moot. Further, Applicants submit that claim 74 as well as new claims 200 to 232 are not anticipated by Brams. To anticipate, a reference must disclose every element of the claims. *Verdegaal Bros. v. Union Oil Co. of California,* 814 F.2d 628, 631 (Fed. Cir. 1987). Claim 74 recites a pharmaceutical composition of palivizumab, or fragments thereof, formulated for pulmonary delivery and new claims 200-230 relate to methods of treatment and prophylaxis using palivizumab or fragments thereof. Palivizumab, as described in the specification, is a humanized antibody directed against RSV.

Brams, on the other hand, discloses methods for making human antibodies by transplanting *in vitro* antigen primed human splenocyte cells into an immunocompromised mouse. Antibodies reactive with the RSV F protein were produced by this method. None of the antibodies disclosed in Brams are palivizumab or an antigen binding fragment thereof. In fact, none of the anti-RSV antibodies disclosed in Brams is a humanized antibody. Since Brams does not disclose every element of the claims, Brams cannot anticipate any of claims 74 or 200-230. Therefore, Applicants respectfully request that the Examiner's rejection based on the Brams *et al.* reference be reconsidered and withdrawn.

The Examiner has also rejected claims 1, 5-6, 9 and 14 under 35 U.S.C. § 102(b) as being anticipated by Johnson *et al.* (*J. Infectious Diseases* 176(5): 1215-1224 (1997); "Johnson"). In particular, the Examiner alleges that Johnson teaches the administration of humanized monoclonal antibodies to high-risk infants intravenously in the amount of 2.5 mg/kg for prevention of RSV infection. Although Applicants do not agree with this rejection, Applicants have canceled claims 1, 5-6, 9 and 14 without prejudice, and

thus the rejection is moot. Applicants further submit that Johnson is not applicable to any of the claims as amended or added herein.

Applicants respectfully submit that the Examiner has not correctly characterized the reference. Contrary to the Examiner's characterization, Johnson does not teach the administration of humanized monoclonal antibodies in any dosage amount or by any route of administration to humans - rather, Johnson is only directed to the administration of humanized monoclonal antibodies to cotton rats. The new claims are directed to methods of administering palivizumab to humans within a specific dosage range, effective to achieve a specified effective serum titer at least twenty (20) days after administering a first dose. Johnson does not disclose administration of humanized monoclonal antibodies to the cotton rat with a specified dose that is effective to achieve a desired effective serum titer at least twenty days after administering said dose. In fact, the cotton rats in Johnson are sacrificed five days after antibody administration (Johnson at page 1217). Accordingly, since Johnson does not disclose each and every element of the claimed invention, Johnson does not anticipate claims 74 and 200-230.

In view of the forgoing, Applicants respectfully submit that the claimed subject matter in the pending claims is novel and the Examiner's rejections under 35 U.S.C. § 102(b) should be withdrawn.

The Rejection Under 35 U.S.C. § 103 Should Be Withdrawn

The Examiner has rejected claims 1-72 and 85-199 under 35 U.S.C. § 103(a) as being obvious over Brams or Johnson in view of MedImmune's SYNAGIS® package insert ("Package Insert") and Johnson (U.S. Patent 5,824,307; "the '307 patent") and Lam *et al.* (*Proceed. Int'l. Symp. Control. Rel. Bioact. Mater.*, 24 (1997); "Lam").

The Examiner alleges that the invention as a whole would have been *prima facie* obvious to one of skill in the art at the time the invention was made. In particular, the Examiner alleges that the asserted novelty of the invention based on limitations such as the superior half-life, antibody/antigen binding and dosage of the antibodies of the instant invention are encompassed by the prior art. The Examiner has invited Applicants to specify any contributions over the antibodies disclosed in the prior art.

Specifically, the Examiner alleges that it would have been *prima facie* obvious to administer the antibody (palivizumab) disclosed in the MedImmune package insert in a combination treatment with the antibodies of Brams or Johnson, in view of the '307 patent

which discloses that a plurality of human antibodies against RSV F epitopes as a treatment or prophylaxis for RSV. The Examiner also alleges that it would have been *prima facie* obvious to modify the treatments of Brams or the '307 patent by packaging them in a sustained release vehicle as taught by Lam. Applicants respectfully traverse.[1]

To find obviousness, there must be a reason or suggestion in the art for carrying out the invention, other than the knowledge learned from the applicant's disclosure. *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). The proper inquiry is whether the art suggests the invention, and whether the art provides one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art and not in the Applicants' disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Prior art references may be combined to render an alleged invention obvious under 35 U.S.C. § 103, but teachings of references can be combined only if there is some suggestion or incentive to do so. *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1575 (Fed. Cir. 1984). Care must be exercised not to use the Applicant's disclosure to fill in the gaps in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991); *In re Grabiak*, 769 F.2d 729 (Fed. Cir. 1985). Thus, an Applicant's own teaching in the application in question cannot constitute a proper basis for formulating obviousness rejections; hindsight reconstruction on the basis of an applicant's disclosure is impermissible. *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995); *In re Ochiai*, 71 F.3d 1565 (Fed. Cir. 1995).

First, Applicants respectfully submit that the claimed subject matter relating to palivizumab or fragments thereof administered in sustained release formulation, with increased half-lives, or at specific doses effective to achieve a desired serum titer at least twenty days after administering said dose is not disclosed by the prior art relied on by the Examiner. In other words, the sustained release composition and the low dose methods are clearly novel.

As acknowledged by the Examiner, Brams and Johnson do not disclose the administration of SYNAGIS® (*i.e.*, palivizumab) or antigen binding fragments thereof in

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[1] While claims 1-72, 111-179, 182-185, 188, and 192-199 have been canceled without prejudice, thereby rendering the Examiner's rejections of said claims moot, Applicants address the Examiner's rejections under 35 U.S.C. § 103(a) and submit that pending claims 85-110, 180, 181, 186-187, and 189-191, and new claims 200-230 are allowable over Brams, Johnson, the MedImmune package insert, the '307 patent, and Lam. Applicants reserve the right to pursue the canceled subject matter in a related application.

sustained release pharmaceutical compositions. Nor do they disclose the administration of SYNAGIS® (*i.e.*, palivizumab) or antigen binding fragments thereof as single agents at effective doses as low as the doses specified in the instant claims. Indeed, as discussed *supra*, Brams does not disclose anything about palivizumab or an antigen binding fragment thereof. Although Johnson does disclose palivizumab, Johnson does not describe its use in humans. Nor does Johnson disclose the use of low doses in humans much less disclose administration of humanized monoclonal antibodies effective to achieve a desired effective serum titer at least twenty days after administration.

The MedImmune package insert for SYNAGIS® ("Package Insert") does not remedy the defects of the primary references. The Package Insert actually teaches away from the methods claimed in that only a dose of 15mg/kg is disclosed, not anything lower. In contrast, the claimed subject matter relates to methods of administering SYNAGIS® or pharmaceutical compositions at a low dose while achieving efficaceous levels of antibody. This is not taught or suggested by the primary references alone or in combination with the Package Insert. Indeed, Applicants wish to emphasize that the Package Insert teaches away from the claimed methods. The Examiner's rejections based on the Package Insert should be reconsidered and withdrawn.

The Examiner also alleges that the claims directed to methods or compositions relating to antibodies in sustained release formulations are obvious over Brams and Johnson over Lam. There is no disclosure or even suggestion in Brams or Johnson that humanized monoclonal antibodies for RSV should be formulated as sustained release compositions. Thus, the primary references lack any suggestion of or motivation to make sustained release RSV antibody formulations. Lam does not remedy the deficiencies of these references.

Lam merely discloses that sustained release formulation for an anti-VEGF Fab fragment. Lam does not disclose or suggest a formulation for the sustained release of a humanized RSV monoclonal antibody such as SYNAGIS®.[2]

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[2] In particular, one of skill in the art would have no motivation to combine the disclosures of Brams or Johnson and Lam. At best, Lam shows that sustained release vehicles for delivery of a VEGF antibody Fab fragment is plausible. Applicants submit that this tenuous disclosure would not motivate one to use (or try) the sustained formulation described in Lam for delivery of SYNAGIS® (*i.e.*, palivizumab) or fragments thereof. Indeed, Brams and Johnson relate to different technology – RSV antibodies – not VEGF Fab fragments. Moreover, the lack of any suggestion of sustained release formulations in either Brams or Johnson makes the combination with Lam legally improper. *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998).

Moreover, Applicants disagree with the Examiner that the Lam formulation is specific for humanized antibodies. Rather, Lam only discloses manipulation of various parameters to develop specific sustained release formulations of a Fab fragment of a recombinant humanized monoclonal VEGF antibody. Indeed, many of the parameters were dependent on factors unique to the anti-VEGF Fab fragment, such the stability and size of the specific anti-VEGF Fab fragment, and would not be expected by one of ordinary skill to be applicable to other humanized monoclonal antibodies or antibody fragments, including SYNAGIS®. Applicants submit that other humanized monoclonal antibodies would have different structure, function, or pharmacokinetics than VEGF antibodies. Thus, one of skill in the art would not be motivated to combine the teachings of Lam with teachings of other humanized monoclonal antibodies, *i.e.*, there would be no motivation to apply the teachings of Lam and incorporate a humanized monoclonal antibody such as palivizumab or a fragment thereof into the sustained release formulation of Lam. Furthermore, based on Lam, one of skill in the art would have no reasonable expectation that the sustained release formulation described in Lam could be successfully used for other humanized monoclonal antibodies. The disclosures provide no expectation of success that a humanized monoclonal antibody other than the anti-VEGF Fab fragment could be incorporated in the sustained formulation disclosed in Lam. Accordingly, the claimed subject matter relating to compositions having sustained release formulation or methods using the same are not encompassed by or rendered obvious by the prior art. Applicants request that the rejections based on Brams and Johnson in view of Lam be reconsidered and withdrawn.

Finally, Applicants submit that the claimed subject matter relates to compositions of palivizumab or fragments thereof and methods of administering palivizumab or fragments thereof. However, Applicants do not concede as alleged by the Examiner that compositions of more than one antibody or methods of administering more than one antibody for treatment or prophylaxis of RSV are disclosed by the teachings of Brams and Johnson in view of the '307 patent. Rather, Applicants have chosen to pursue subject matter relating to compositions of more than one antibody or methods comprising administering more than one antibody for treatment or prophylaxis of RSV in a related application. Applicants also do not concede that the teachings of Brams and Johnson in view of the Package Insert disclose compositions comprising antibodies having increased half-lives or methods of administering antibodies having increased half-lives. However, in the interest of expediting prosecution,

Applicants have chosen to pursue subject matter relating to such compositions and methods in a related application.

In view of the foregoing, Applicants submit that the claimed subject matter is not disclosed by the prior art. Applicants request that the rejection of the claims under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

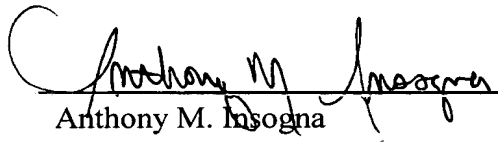
CONCLUSION

Applicants respectfully request that the above-made amendments and remarks be entered and made of record in the file history of the present application. Claims 73, 74, 83-110, 180, 181, 186-187, 189-191, and 200-230 fully meet all statutory requirements for patentability. Withdrawal of the Examiner's rejections, and allowance and action for issuance, are respectfully requested.

Applicants respectfully request that the Examiner call the undersigned at (212) 790-6293 if any questions or issues remain.

Respectfully submitted,

Date September 26, 2002



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